

Draft Guidance on Potassium Chloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Potassium Chloride

Form/Route: Extended Release Capsules/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 10 mEq x 8 capsules (80 mEq)
Subjects: Healthy males and non-pregnant females, general population.
Additional Comments: Please see specific recommendations regarding the fasting bioequivalence study below.

2. Type of study: Fasting sprinkle-in-applesauce
Design: Single-dose, two-way crossover in vivo
Strength: 10 mEq x 8 capsules (80 mEq)
Subjects: Healthy males and non-pregnant females, general population.
Additional Comments: Please see specific recommendations regarding the fasting sprinkle bioequivalence study below.

Analytes to measure (in appropriate biologic fluid): Potassium in urine

Bioequivalence based on (90% CI): Baseline-adjusted potassium.

Waiver request of *in-vivo* testing: 8 mEq based on (i) acceptable bioequivalence studies on the 10 mEq strength, (ii) acceptable in-vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at <http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm>. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be

submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Specific recommendations regarding fasting and fasting sprinkle bioequivalence (BE) studies:

NOTE: The recommendations for both fasting and fasting sprinkle studies are the same except for the additional dietary conditions during diet equilibration period and on dosing dates (for the fasting sprinkle study).

1. Inclusion/Exclusion Criteria

It is recommended that the applicant include a sufficient number of subjects in the study to demonstrate bioequivalence. Subjects eligible to participate should be between the ages of 20 and 40 years and be within ± 10 percent of ideal body weight. Study subjects should be asked not to undertake vigorous physical exercise beginning 7 days before the start of the study period and continuing until discharge from the clinic. They should also be asked not to consume alcoholic beverages for a period beginning 48 hours before drug administration and ending after study completion.

Subjects with any of the following conditions would be excluded from the study:

- Obvious signs of serious renal, gastrointestinal, cardiovascular, hepatic, neurological, or adrenopituitary disorders, as evidenced by medical examination, physical examination, and/or clinical laboratory tests
- Use of tobacco in any form, currently or within the 6 months before study initiation
- Use of any known enzyme inducers or inhibitors within 30 days before study entry
- History of drug or alcohol abuse
- History of hypersensitivity to the drug or similar compounds
- Use of any prescription or nonprescription (over-the-counter (OTC)) medication within 2 weeks before study entry

2. Dietary and Housing Considerations

The subjects should be placed on a standardized diet, with known amounts of potassium, sodium, calories, and fluid intake. The fluid intake should be maintained at 3,000 to 5,000 milliliters (mL) per day to ensure an adequate rate of urine flow throughout the study period. This is higher than the normal fluid intake of 1,300 to 2,500 mL per day. Strict control and knowledge of the actual intakes of potassium, sodium, calories, and fluid are critical for study success. Detailed information regarding the composition of the diet should be included in the final report.

Study subjects should be placed in a climate-controlled environment, remaining in-house as much as possible. Physical activity should be restricted to avoid excessive sweating and thus potassium loss. Meals, snacks, and fluids should be given at standard times, and subjects strongly encouraged to ingest the recommended amounts while refraining from unnecessary physical activity. In addition, subjects should be queried regarding any prolonged episodes of diarrhea

or excessive sweating, as these occurrences may invalidate or obscure the results. A test for fecal occult blood should be performed on each dosing day.

3. Collection of Urine and Blood Samples

The volume of each urine collection should be recorded. Aliquots of each urine collection should be stored frozen until assayed for potassium. Creatinine clearance should be determined to ensure that urine collection has been adequate. After the aliquots are drawn, all remaining urine samples for each subject over a 24-hour period can be pooled for urine creatinine determination. A blood sample should be drawn at approximately the same time each day for serum creatinine determination. The usual time to collect blood samples for creatinine determination is at the mid-point of the urine collection.

4. Study Design

It is recommended that the study be conducted over a single period of residence in the clinic, the duration of which is 16 days and 17 nights. This time would be divided into two 8-day periods, with dose administration to take place on days 7 and 15. Recommended study procedures are identical for each of the 8-day periods (see Appendix). The recommended schedule for study periods 1 and 2 follows:

Diet Equilibration Days, Days 1-4 and 9-12

- Diets should be standardized to provide the following daily intake of potassium, sodium, and calories:

Potassium: 50-60 mEq
Sodium: 160-180 mEq
Calories: 2500-3500

- Fluids should be administered according to the following schedule:

500 mL of room temperature water initially (at 07:00 hours) 200 mL every hour afterwards for 12 hours
Additional (known) amounts of fluid can be administered at the investigator's discretion from 19:00 hours until 07:00 hours the following day

- No urine is collected during the diet equilibration days

Baseline Days, Days 5-6 and 13-14

- The standard diet and fluid schedule should continue as described for the equilibration days.
- Urine should be collected each day to establish each subject's baseline level of potassium excretion.
- Urine collection intervals should be at hours 0-1, 1-2, 2-4, 4-6, 6-8, 8-12, 12-16 and 16-24.

- Urine collection should begin at 07:00 hours. On days 5 and 13, subjects can dispose of this sample. On days 6 and 14, the urine collected at 07:00 hours completes the 16-24 hour sample.
- Blood samples for creatinine clearance determination should be collected on days 6 and 14.

Additional Dietary Conditions for the Fasting Sprinkle Study

Subjects should consume the same amount (i.e., a tablespoon) of room temperature applesauce (from the same batch number) on Diet Equilibration Days 1-4 (period 1) and 9-12 (period 2) and on Baseline Days 5-6 (period 1) and 13-14 (period 2), at the same time corresponding to the planned dosing time on days 7 and 15.

Drug Dosing Days, Days 7 and 15

- *For the Fasting BE Study:* After an 8-hour overnight fast, 80 mEq of either test or reference product should be given by mouth at 07:00 hours with 500-mL room temperature water.
- *For the Fasting Sprinkle BE Study:* After an 8-hour overnight fast, the entire content of an 80 mEq capsule of either the test or reference product should be sprinkled on a tablespoon of room temperature applesauce and given by mouth, at 7:00 hours, followed by 500-mL room temperature water. The applesauce should be swallowed without chewing, immediately or not more than 5 minutes after being sprinkled with the capsule content.
- Subjects should remain upright (sitting upright, standing, or slowly walking) for at least 3 hours following dosing.
- The standard diet and fluid schedule should continue as described for the equilibration days.
- Urine collection times should be the same as on days 5, 6, 13, and 14.
- Blood samples should be collected for creatinine clearance determination.
- Fecal blood determinations should be made on each bowel movement. *Post-*

Drug Dosing Days, Days 8 and 16

- The standard diet and fluid schedule should continue as described for the equilibration days.

Discharge, Day 17

- Subjects can be discharged following the final urine collection at 07:00 hours.

5. Clinical Reports and Adverse Reactions

Patient medical histories, physical examination reports, and all incidents of possible adverse reactions should be reported.

6. Baseline Adjustment and Data Analysis

Baseline excretion of potassium (obtained during the baseline days) should be subtracted from the amount obtained on the drug dosing day to yield the net effect of drug administration. The baseline data used should be the average of the two readings obtained on the two baseline days and be subject specific and period specific (e.g., for subject #12, his or her **period II** amount of baseline excretion would **only** be used to adjust his or her **period II** drug dosing day amount).

The following information on urine potassium concentration data should be recorded for each subject:

- Amount excreted in each collection interval (Ae)
- Cumulative urinary excretion from 0 to 24 hours (Ae0-24h)
- Cumulative urinary excretion from 0 to 48 hours (Ae0-48h)
- Maximal rate of urinary excretion (Rmax)
- Time of maximal urinary excretion (Tmax)
- Excretion rate in each collection interval (R)
- Midpoint of each collection interval (t)

All data should be calculated using baseline-adjusted and nonbaseline-adjusted data. Statistical analysis ($p=0.05$) should be done by ANOVA for baseline-adjusted parameters, and the 90 percent confidence intervals should be generated for natural log-transformed cumulative urinary excretion from 0 to 24 hours (Ae0-24h) and maximal rate of urinary excretion data (Rmax). The two one-sided tests procedure can be used to determine 90 percent confidence intervals